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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,444	09/18/2000	John C Bell	18003	4773

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Lewis J Kreisler
Legal Department
930 Clopper road
Gaithersburg, MD 20878

EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/664,444	BELL ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19 and 24-63* is/are pending in the application.

4a) Of the above claim(s) *2-4,14-17 and 38-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-13,19 and 24-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-17,19 and 24-63* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-29-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 12-19-2003 are acknowledged. Claim 18 has been canceled. Claims 1-17, 19 and 24-63 are pending. Claims 2-4, 14-17 and 38-63 remain withdrawn from consideration. Claims 1, 5-13, 19 and 24-37 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed on 12-19-2003 is acknowledged. An initialed copy is attached hereto.

Priority

Applicant has met the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. The amendment originally dated 3-14-2002 (now dated 12-29-2003) is acknowledged and made of record.

Claim Rejections Withdrawn

The rejection of claim 18 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "substantially no PKR activity" is withdrawn. Cancellation of said claim has rendered the rejection moot.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The instant claims are drawn to methods of reducing the viability of hematopoietic tumor cells by administering a virus and optionally interferon.

The rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record. The cancellation of claim 18 has rendered the rejection of said claim moot.

As set forth in the previous Office action, the specification, while being enabling for methods utilizing **VSV** for reducing the viability of mylogenous leukemia cell lines *in vitro*, does not provide enablement for the utilization of **VSV** for the reduction of viability of all hematopoietic tumor cells (either *in* vivo or *in vitro*). The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Applicant argues:

1. The Office has improperly placed on applicants the burden of proving their invention works.
2. Applicants are not required to submit experimental results demonstrating the anti-tumor activity of vesicular stomatitis virus.

3. The instant rejection is based on the alleged failure to "name" a sufficient number of hematopoietic tumor cells.

4. The Office has improperly tried to place on Applicant the burden of proving that the invention works *in vivo*. Moreover, the specification does contain *in vivo* data demonstrating the efficacy in treating human melanoma xenographs in nude mice (Example 25, page 49)

5. The Office is improperly requiring Applicant to provide evidence necessary to overcome the more stringent requirements under the Food and Drug act for approval to market a particular drug for human consumption.

6. Applicant assert that it is accepted in the art to which the invention pertains that *in vitro* evidence of anti-tumor effect is reasonably correlated to *in vivo* efficacy as illustrated by Percora et al. (J. Clinical Oncology, Vol. 20, No. 9, 2002, pages 2251-2266).

7. McCormick (U.S. patent 5,677,178) bases its teaching of human therapy solely on *in vitro* results.

8. The articles cited by the Office merely illustrate that an *in vitro* experiment cannot duplicate the *in vivo* environment exactly. Moreover, if there were not clinical correlations between *in vitro* experiments and *in vivo* efficacy, the *in vitro* experiments would not be so widely used.

9. The Office has improperly sought to place on Applicants the burden of explaining the mechanism by which the claimed invention works i.e. the office has required Applicant to explain how the viruses of the claimed invention enter the cells they infect.

10. The instant invention is not limited to tumor cells that lack PKR activity.

11. The claimed invention as claimed does not rest on the selection of certain types of interferon or (other than claim 32) the route of administration.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Applicant's assertion that Applicant is not required to demonstrate that their claimed invention works nor are they required to submit experimental results demonstrating the anti-tumor of vesicular stomatitis virus (points 1 and 2), Applicant is reminded that a conclusion of lack of enablement means that the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without **undue experimentation**. As outlined in the previous Office action, the instant claims are drawn to using VSV to **all** forms of hematopoietic tumor cells, while the specification is silent on what hematopoietic tumor cells (other than a few cell lines) are susceptible to the anti-tumor effect of VSV and is equally silent on how said virus is to be administered. Applicant argues that all methodologies known in the art would be effective. This however, contradicts Applicant's assertion in the Specification. Applicant states on page 33 of the specification that PKR-/- mice were killed with VSV by several routes of infection but that these mice were not affected by intravenous injections of the virus. This illustrates that the route of administration, contrary to Applicant's assertion to the contrary, has an affect on the biological effects of VSV *in vivo.* Moreover, there is a marked difference in the efficacy of delivering a therapeutic agent to a solid tumor cell as opposed to a leukemia cell. Jain discloses the art known barriers to the delivery of drugs into solid tumors (Scientific American Vol 271 No. 1, pages 58-65, July 1994). Impediments to drug delivery include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased

viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61) and (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1). Therefore, contrary to Applicant's assertion to the contrary, the method of administration would vary depending on the tumor type and location of said tumor.

With regard to Point 3, contrary to Applicant's assertion, the rejection is based (in part) on the failure of the specification to provide guidance as to which hematopoietic tumor cells **are susceptible to the anti-tumor effect of VSV**. This is quite different from a recitation of which cells would be histologically classified as being hematopoietic in origin.

With regard to Point 4, the example recited by Applicant is insufficient to provide enablement for the full breadth of the instant claims. Firstly, the xenographs utilized in Example 25 (on page **50** of the specification), comprise a cell line (SK-Mel3). Secondly, said example only utilizes two of the five VSV mutants disclosed in the instant Specification lending support to the unpredictability of the anti-tumor effect of VSV. Thirdly, the instant claims are drawn to use of VSV to reduce the viability of a hematopoietic tumor cell whereas Example 25 demonstrates only that two mutated VSV viruses can reduce the viability of cell-line based xenographs in immunodeficient mice. This cannot be extrapolated to the use of wild-type (non-mutated) VSV against established tumors in an immunocompetent animal.

With regard to Point 5, contrary to Applicant's assertion, the Office is not requiring Applicant to demonstrate that the claimed VSV composition is "safe and effective" as required by the Food and Drug Act, merely that the application of said composition to an individual is beneficial to said individual.

With regard to Applicant's assertion that it is accepted in the art to which the instant invention pertains that *in vitro* evidence of anti-tumor effect is reasonably correlated to *in vivo* efficacy (point 6), those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. Contrary to Applicant's assertion (Point 8), the cited references illustrate that there is not a predictable correlation between *in vitro* assays and *in vivo* efficacy. As outlined previously, the greatly increased **complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability**. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*).

Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, **"petri dish cancer" is a poor representation of malignancy**, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

With regard to Applicant's assertion that Percora et al. (J. Clinical Oncology, Vol. 20, No. 9, 2002, pages 2251-2266) and McCormick (U.S. Patent 5,677,178 demonstrate that oncolytic viruses can have therapeutic effect *in vivo* (Point 6 and 7), Applicant is reminded that neither Percora et al. nor McCormick disclose the use of VSV for the treatment of hematopoietic tumor cells. Moreover, it is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini, 21 USPQ2d 1892, 1897 (BPAI 1991).

With regard to Point 9, the reference the Specifications silence with regard to what receptor was utilized by VSV was merely an illustration of the total lack of guidance provided by the specification with regard to what types of hematopoietic tumor cells could be treated by the methodologies of the instant invention.

With regard to Points 10-11, it is acknowledged that the instant claims are not limited to either tumor cells that lack PKR activity or the use of alpha interferon. However, it should be noted that the specification only provides guidance for the selective *in vitro* killing of a few PKR – cell lines. Additionally, the specification is silent on the optional use of any interferon other than alpha interferon. Moreover, contrary to Applicant's assertion, the Office is not requiring the naming of all the different types of interferon, to provide guidance as to which interferons other than alpha interferon **would provide normal cells protection from viral infection**.

Consequently, as outlined in the previous Office action, the specification, while being enabling for methods utilizing **VSV** for reducing the viability of mylogenous leukemia cell lines *in vitro*, does not provide enablement for the utilization of **VSV** for the reduction of viability of all hematopoietic tumor cells (either *in* vivo or *in vitro*). The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

The rejection of claims 1 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "administering to the tumor cell a virus" is maintained for reasons of record.

Applicant argues:

1. In accordance with the instant invention, the virus can be administered to the tumor cell utilizing any conventional technique.

2. Breadth is not to be equated with indefiniteness.

3. One of ordinary skill in the art would know whether he is administering the cell or not.

Applicant's arguments have been fully considered and deemed non-persuasive. It is still unclear what is meant by said phrase. What are considered to be conventional methods of "administering"? Contrary to Applicant's assertion, the skilled artisan would not be able to determine the metes and bounds of the claimed invention. The instant claim encompasses *in vivo* treatment methods. How does one specifically administer VSV directly "to the tumor cell" when said cell resides within an individual.

The rejection of claims 24 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "administering interferon to the tumor cell" is maintained for reasons of record.

Applicant argues:

1. In accordance with the instant invention, the virus can be administered to the tumor cell utilizing any conventional technique.

2. Breadth is not to be equated with indefiniteness.

3. One of ordinary skill in the art would know whether he is administering the cell or not. Applicant's arguments have been fully considered and deemed non-persuasive. It is still unclear what is meant by said phrase. What are considered to be conventional methods of "administering"? Contrary to Applicant's assertion, the skilled artisan would not be able to determine the metes and bounds of the claimed invention. The instant claim encompasses *in vivo* treatment methods. How does one specifically administer interferon directly "to the tumor cell" when said cell resides within an individual.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Zeman
May 17, 2004

L. R. F. Smith

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600